1,129,210

PATENT SPECIFICATION

NO DRAWINGS **1,129,210**

Date of Application and filing Complete Specification: 6 April, 1967.
No. 10391/68.
Application made in Germany (No. B86610 IVb/12o) on 9 April, 1966.
(Divided out of No. 1,129,209).
Complete Specification Published: 2 Oct., 1968.

F29Y,
F360,

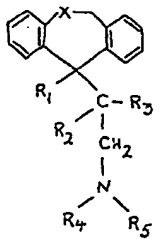
ERRATA

SPECIFICATION No. 1,129,210

Page 1, lines 33 and 34, *for* "his-aminolytic" *read* "histaminolytic"
Page 3, line 76, *after* "6H" *delete* "1", *for* "-thiocene." *read* "-thiocine."
Page 3, line 101, *after* "alkyl" *insert* "radical"

THE PATENT OFFICE
16th December 1968

ing to the present invention are compounds of the general formula:—



(I)

wherein X is an oxygen or sulphur atom or an ethylene or thiomethylene group, R_1 is a hydrogen atom or a hydroxyl group, R_2 and R_3, which may be the same or different, are hydrogen atoms or alkyl radicals containing up to 3 carbon atoms, R_5 is an alkyl radical containing up to 3 carbon atoms, and R_4 is a hydrogen atom or R_1 and R_2 together represent a further valency bond, with the proviso that when X is an oxygen atom and R_1 and R_2 together represent a further valency bond, then R_3 must be an alkyl radical; and the addition salts thereof with organic or inorganic acids.

We have found that the new compounds of general formula (I) exhibit a wide pharmacological spectrum of activity and, in par-

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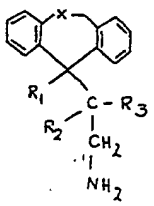
(II)

wherein R_1, R_2, R_3, R_4, R_5 and X have the same meanings as above, by reduction of the amido group to an amino group and, if desired, when R_1 is a hydroxyl group, the compounds can, before or after reduction of the amido group, be dehydrated and thereafter, if desired, the double bond so formed can be reduced and, if desired, when R_4 is an alkyl radical, this substituent can be subsequently introduced or split off.

The new compounds according to the present invention can also be prepared by N-alkylating compounds of the general formula:



(III)

in which X, R_1, R_2 and R_3 have the same meanings as above, in the manner known from the literature for the alkylation of amines.

SEE ERRATA SLIP ATTACHED

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Index at acceptance:—C2 C(2A2, 2A3, 2A5, 2A6, 2A9, 2A14, 2R16, 2R17, LF29X, LF29Y, LF32Y, LF36Y, LF43X, LF45Y, LF213, LF253, LF254, LF323, LF360, LF363, LF450, LF455, LF456, LF672)

Int. Cl.:—C 07 c 87/02, C 07 d 9/00, C 07 d 67/00

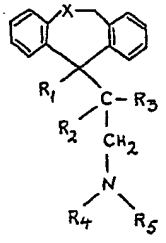
COMPLETE SPECIFICATION

Tricyclic N-Alkylated Derivatives of Ethylamine

We, C. F. BOEHRINGER & SOEHNE G.M.B.H., of Mannheim-Waldhof, Germany, a Body Corporate organised under the laws of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to particularly described in and by the following statement:—

The present invention is concerned with new tricyclic N-alkylated derivatives of ethylamine and with the preparation thereof.

The new derivatives of ethylamine according to the present invention are compounds of the general formula:—

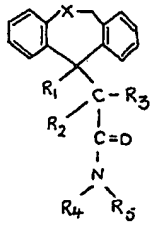


(I)

wherein X is an oxygen or sulphur atom or an ethylene or thiomethylene group, R_1 is a hydrogen atom or a hydroxyl group, R_3 and R_4, which may be the same or different, are hydrogen atoms or alkyl radicals containing up to 3 carbon atoms, R_5 is an alkyl radical containing up to 3 carbon atoms, and R_2 is a hydrogen atom or R_1 and R_2 together represent a further valency bond, with the proviso that when X is an oxygen atom and R_1 and R_2 together represent a further valency bond, then R_3 must be an alkyl radical; and the addition salts thereof with organic or inorganic acids.

We have found that the new compounds of general formula (I) exhibit a wide pharmacological spectrum of activity and, in particular, possess sedative, anti-convulsive, hisaminolytic or broncholytic properties.

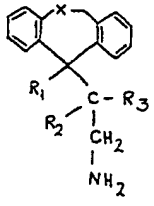
The new compounds according to the present invention can be prepared from compounds of the general formula:—



(II)

wherein R_1, R_2, R_3, R_4, R_5 and X have the same meanings as above, by reduction of the amido group to an amino group and, if desired, when R_1 is a hydroxyl group, the compounds can, before or after reduction of the amido group, be dehydrated and thereafter, if desired, the double bond so formed can be reduced and, if desired, when R_4 is an alkyl radical, this substituent can be subsequently introduced or split off.

The new compounds according to the present invention can also be prepared by N-alkylating compounds of the general formula:



(III)

in which X, R_1, R_2 and R_3 have the same meanings as above, in the manner known from the literature for the alkylation of amines.

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The dehydration of compounds in which R_1 is a hydroxyl group to give compounds in which R_1 and R_2 together represent an additional valency bond, is carried out in known manner, for example by heating in alcoholic hydrochloric acid. By the reduction of the double bond so formed, for example with amalgamated alumium powder, there are obtained compounds (I) in which R_1 and R_2 are both hydrogen atoms. The reduction of the amido group to an amino group is also carried out in known manner with, for example, a complex metal hydride, preferably lithium aluminium hydride.

When R_4 in the products obtained is an alkyl radical, this can, if desired, be split off to give the corresponding monoalkylated compound. For this purpose, compounds (I) in which R_4 signifies an alkyl radical are first reacted with a chloroformic acid ester and then heated with an alcoholic solution of potassium hydroxide.

In principle, however, it is also possible to proceed the other way round in that monoalkylated compounds (I), i.e. the compounds in which R_4 is a hydrogen atom, are subsequently N-alkylated in known manner in order to give compounds (I) in which R_4 is an alkyl radical. In this case, preferred alkylation agents are the alkyl halides and reactive derivatives of carboxylic acids containing up to 3 carbon atoms, whereby, in the latter case, the initially formed N-acyl derivatives are subsequently reduced to the N-alkyl derivatives.

Instead of the monoalkylated compounds (I), i.e. the compounds in which R_4 is a hydrogen atom, there can also be used the compounds (III) for the subsequent alkylation according to the present invention. In this case depending upon the reaction conditions, there are obtained, in known manner, the mono- and di-alkylated compounds (I), i.e. compounds in which R_4 is either a hydrogen atom or an alkyl radical. For example, with typical alkylation agents, such as alkyl halides, there are preferentially obtained the dialkyl derivatives, i.e. those in which R_4 is alkyl radical, from which an alkyl radical can again be split off. However, it is certainly also possible directly and selectively to obtain only the monoalkyl derivatives, i.e. those in which R_4 is a hydrogen atom, by preparing the monoacyl derivatives and subsequently reducing them or by first introducing, before the N-alkylation with alkyl halides, a protective group which can be readily split off, such as a benzoyl or tosyl group, which is subsequently removed hydrolytically.

The compounds (II) used as starting materials are described and claimed in our Specification No. 15817/67, Serial No. 1129209, and the compounds (III) used as starting materials are described and claimed in our Specification No. 10849/67, Serial No. 1129029.

The following Examples are given for the purpose of illustrating the present invention:

EXAMPLE 1.

11 - hydroxy - 11 - (2 - dimethylaminoethyl) - 6,11 - dihydro - dibenzo - [b,e] - oxepin.

6 g. 11 - hydroxy - 11 - (N,N - dimethylcarboxamido - methyl) - 6,11 - dihydro - dibenzo - [b,e] - oxepin (0.02 mol), prepared in the manner described in Example 1 of Specification No. 15817/67, Serial No. 1129209, are dissolved in 100 ml. ether and added dropwise at 0—10°C. to an ethereal suspension of 1.55 g. lithium aluminium hydride (0.04 mol) in 50 ml. ether. After stirring for 4 hours at a maximum temperature of 10°C., the reaction mixture is mixed with a saturated, aqueous solution of sodium chloride until the hydroxide precipitations agglomerate and the inorganic material is then filtered off with suction. The 11 - hydroxy - 11 - (2 - dimethylaminoethyl) - 6,11 - dihydro - dibenzo - [b,e] - oxepin formed is precipitated out of the ethereal solution as the maleate; m.p. 156—157°C.; yield 6.6 g. (82.5% of theory). This is subsequently mixed with a solution of sodium hydroxide, extracted with ether and the hydrobromide is precipitated out with ethereal hydrobromic acid. The yield is 5 g. (68.7% of theory); m.p. 214—215°C., after recrystallisation from ethanol.

EXAMPLE 2.

11 - hydroxy - 11 - (2 - dimethylaminoethyl) - 6,11 - dihydro - dibenzo - [b,e] - thiepin.

In a manner analogous to that described in Example 1, from 11 - hydroxy - 11 - (N,N - dimethylcarboxamido - methyl) - 6,11 - dihydro - dibenzo - [b,e] - thiepin, prepared according to Example 2 of Specification No. 15817/67, Serial No. 1129209, there is obtained, by reduction with lithium aluminium hydride, 11 - hydroxy - 11 - (2 - dimethylaminoethyl) - 6,11 - dihydro - dibenzo - [b,e] - thiepin. The yield is 58% of theory (as the hydrochloride); m.p. 245°C., after recrystallisation from methanol.

EXAMPLE 3.

11 - (2 - dimethylaminoethylidene - 1) - 6,11 - dihydro - dibenzo - [b,e] - thiepin.

0.3 mol of the hydroxy compound prepared according to Example 2 is dehydrated by boiling for one hour with 100 ml. ethanolic hydrochloric acid. The residue obtained by evaporation of the reaction mixture is treated with aqueous soda lye to set free the base, which is extracted with ether. The residue obtained by evaporation of the ethereal phase is dissolved in isopropanol and treated with ethereal hydrochloric acid. In this way, there is obtained the hydrochloride of 11 - (2 - dimethylaminoethylidene - 1) - 6,11 - dihydro - dibenzo - [b,e] - thiepin in a yield of 76%; m.p. 232—233°C., after recrystallisation from iso-

propanol. The free base has a boiling point of 160—162°C./0.05 mm.Hg.

EXAMPLE 4.

11 - (2 - dimethylaminoethyl) - 6,11 - dihydro - dibenzo - [b,e] - oxepin.

0.01 mol 11 - (N,N - dimethylcarboxamido - methyl) - 6,11 - dihydro - dibenzo - [b,e] - oxepin, prepared according to Example 5 of Specification No. 15817/67, Serial No. 1129209, is stirred for 3 hours at 0—10°C. in 250 ml. ether with 0.06 mol lithium aluminium hydride. The reaction mixture is subsequently mixed with a saturated solution of sodium chloride, the precipitated hydroxides filtered off with suction and, by adding maleic acid dissolved in tetrahydrofuran, to the organic phase, there is precipitated out the maleate of 11 - (2 - dimethylaminoethyl) - 6,11 - dihydro - dibenzo - [b,e] - oxepin; yield 90% of theory; m.p. 152—153°C., after recrystallisation from isopropanol.

EXAMPLE 5.

11 - (2 - dimethylaminoethyl) - 6,11 - dihydro - dibenzo - [b,e] - thiepin.

In a manner analogous to that described in Example 4 by the reduction of 11 - (N,N - dimethylcarboxamido - methyl) - 6,11 - dihydro - dibenzo - [b,e] - thiepin, prepared according to Example 6 of Specification No. 15817/67, Serial No. 1129209, there is obtained 11 - (2 - dimethylaminoethyl) - 6,11 - dihydro - dibenzo - [b,e] - thiepin in a yield of 81% of theory; m.p. of the hydrochloride 201—202°C., after recrystallisation from methylene chloride and ether.

EXAMPLE 6.

11 - (2 - monomethylaminoethyl) - 6,11 - dihydro - dibenzo - [b,e] - oxepin.

0.04 mol of the compound prepared according to Example 4 is boiled for one hour with 10 ml. chloroformic acid ethyl ester and 50 ml. benzene. Subsequently, the reaction is evaporated to dryness and the residue obtained boiled under reflux for 12 hours with 13 g. potassium hydroxide in 60 ml. ethanol, diluted with water, extracted with ether and the hydrochloride of 11 - (2 - monomethylaminoethyl) - 6,11 - dihydro - dibenzo - [b,e] - oxepin precipitated out of the ethereal solution. After recrystallisation from isopropanol, the yield is 55% of theory; m.p. 215—216°C.

EXAMPLE 7.

12 - (2 - dimethylamino - ethylidene) - 5,6,7,12 - tetrahydro - dibenzo - [a,d] - cyclooctene.

0.05 mol 12 - (N,N - dimethylcarboxamido - methylene) - 5,6,7,12 - tetrahydro - dibenzo - [a,d] - cyclooctene, prepared according to Example 8 of Specification No. 15817/67, Serial No. 1129209, together with 0.05 mol lithium aluminium hydride, are dissolved in tetrahydrofuran and stirred for 2 hours at ambient temperature. After the addition of a saturated solution of sodium chloride, the precipitated metal hydroxides are filtered off with suction and the crude base isolated from the organic phase is converted into the hydrochloride. The yield of 12 - (2 - dimethylamino - ethylidene) - 5,6,7,12 - tetrahydro - dibenzo - [a,d] - cyclooctene is 81% of theory. The hydrochloride has a melting point of 188—189°C., after recrystallisation from isopropanol.

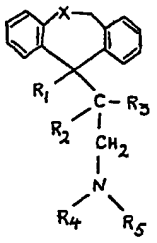
EXAMPLE 8.

12 - (2 - dimethylamino - ethylidene) - 7,12 - dihydro - 6H 1 dibenzo - [b,e] - thiocene.

In a manner analogous to that described in Example 1, by the reduction with lithium aluminium hydride of 12 - hydroxy - 12 - (N,N - dimethylcarboxamido - methyl) - 7,12 - dihydro - 6H - dibenzo - [b,e] - thiocine, prepared according to Example 9 of Specification No. 15817/67, Serial No. 1129209, and subsequent dehydration with ethanolic hydrochloric acid in the manner described in Example 3, there is obtained 12 - (2 - dimethylamino - ethylidene) - 7,12 - dihydro - 6H - dibenzo - [b,e] - thiocine in 63% yield; m.p. 198—200°C. in the form of the hydrochloride, after recrystallisation from isopropanol.

WHAT WE CLAIM IS:—

1. Tricyclic N-alkylated derivatives of ethylamine of the general formula:—



wherein X is is an oxygen or sulphur atom or an ethylene or thiomethylene radical, R_1 is a hydrogen atom or a hydroxyl group, R_3 and R_4, which may be the same or different, are hydrogen atoms or alkyl radicals containing up to 3 carbon atoms, R_5 is an alkyl containing up to 3 carbon atoms and R_2 is a hydrogen atom or R_1 and R_2 together represent a further valency bond, with the proviso that when X is an oxygen atom and R_1 and R_2 together represent a further valency bond then R_3 must be an alkyl radical; and the addition salts thereof with inorganic and organic acids.

2. 11 - hydroxy - 11 - (2 - dimethylaminoethyl) - 6,11 - dihydro - dibenzo - [b,e] - oxepin.

3. 11 - hydroxy - 11 - (2 - dimethylaminoethyl) - 6,11 - dihydro - dibenzo - [b,e] - thiepin.

4. 11 - (2 - dimethylaminoethylidene - 1) - 6,11 - dihydro - dibenzo - [b,e] - thiepin.

5. 11 - (2 - dimethylaminoethyl) - 6,11 - dihydro - dibenzo - [b,e] - oxepin.

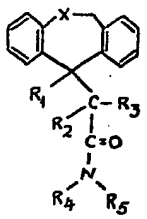
6. 11 - (2 - dimethylaminoethyl) - 6,11 - dihydro - dibenzo - [b,e] - thiepin.

7. 11 - (2 - monomethylaminoethyl) - 6,11 - dihydro - dibenzo - [b,e] - oxepin.

8. 12 - (2 - dimethylamino - ethylidene) - 5,6,7,12 - tetrahydro - dibenzo - [a,d] - cyclooctene.

9. 12 - (2 - dimethylamino - ethylidene) - 7,12 - dihydro - 6H - dibenzo - [b,e] - thiocine.

10. Process for the preparation of compounds of the general formula given in claim 1, wherein a compound of the general formula: —



in which R_1, R_2, R_3, R_4, R_5 and X have the same meanings as in claim 1, is reduced to convert the amido group into an amino group and, if desired, when R_1 is a hydroxyl group, the compound is, before or after reduction of the amido group, dehydrated and thereafter, if desired, the double bond so formed is reduced and, if desired, when R_4 is an alkyl radical, this substituent is subsequently introduced or split off.

11. Process according to claim 10, wherein the dehydration is carried out by heating in alcoholic hydrochloric acid.

12. Process according to claim 10 or 11, wherein the double bond is reduced with amalgamated aluminium powder to give a compound in which R_1 and R_2 both represent hydrogen atoms.

13. Process according to any of claims 10—12, wherein the amido group is reduced with a complex metal hydride.

14. Process according to claim 13, wherein the complex metal hydride is lithium aluminium hydride.

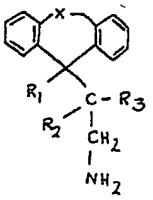
15. Process according to any of claims 10—14, wherein a compound in which R_4 is an alkyl radical is first reacted with a chloroformic acid ester and then heated with an alcoholic solution of potassium hydroxide to give the corresponding compound in which R_4 is a hydrogen atom.

16. Process according to any of claims 10—14, wherein a compound in which R_4 is a hydrogen atom is N-alkylated with an alkylating agent.

17. Process according to claim 16, wherein the alkylating agent is an alkyl halide.

18. Process according to claim 16, wherein the N-alkylation is carried out by first reacting with a carboxylic acid derivative containing up to 3 carbon atoms to give the corresponding N-acyl derivative which is thereafter reduced.

19. Process for the preparation of compounds of the general formula given in claim 1, wherein a compound of the general formula: —



in which R_1, R_2, R_3 and X have the same meanings as in claim 1, is N-alkylated.

20. Process according to claim 19, wherein the N-alkylation is carried out with the use of an alkyl halide to give the corresponding N,N - dialkyl compound, from which, if desired, an alkyl radical is split off by the method according to claim 15 to give the corresponding compound in which R_4 is a hydrogen atom.

21. Process according to claim 19, wherein there is first prepared the corresponding monoacyl derivative which is, in turn, reduced to give the corresponding monoalkyl compound in which R_4 is a hydrogen atom.

22. Process according to claim 19, wherein a protective group is first added to the nitrogen atom of the amino group, the resultant compound then N-alkylated with an alkyl halide and the protective group thereafter split off to give a product in which R_4 is a hydrogen atom.

23. Process according to claim 22, wherein the protective group is a benzoyl or tosyl group which is subsequently removed hydrolytically.

24. Process for the preparation of compounds of the general formula given in claim 1, substantially as hereinbefore described and exemplified.

25. Compounds of the general formula given in claim 1, whenever prepared by the process according to any of claims 10—24.

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